Clinical Chemistry

A Retrospective Look at Routine Screening

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RECENTLY THERE HAS BEEN a surge of interest in automated clinical chemistry and of routine blood chemistry screening tests. Chemistry panels are being advocated for routine hospital admission studies, periodic health examinations, routine diagnostic surveys, detection of pre-disease, chemical fingerprinting and predictive medicine.

Enthusiasm has been expressed for these screening tests since costs seem reasonable and the incidence of abnormal findings seems to be great. Cost reductions are realized in doing large numbers of tests with multi-channel analysis. However, fewer test channels might well be done more cheaply. The extra cost for more test channels may not be justified if these additional studies do not provide information significantly useful to the particular patient.

Good medicine should not relate only to cost but primarily to good patient care. For example, if a routine admission study included a blood glucose and urea so that occult diabetes mellitus or renal insufficiency might be detected, it may not be pertinent to do routinely determinations of, say, sodium, chloride, carbon dioxide content and acid phosphatase, just because they can be done at little extra cost. It is already obvious from general surveys that there is no practical value in doing a serum acid phosphatase determination in a health evaluation screening study, and sodium, potassium, chloride and carbon dioxide content may also be of no value.

Literature and personal communications are reviewed in this paper in an attempt to determine if routine chemistry screening was in the interests of the best practice of medicine. It was apparent in the beginning of this study that optimistic reports on the value of chemistry screening did not give enough consideration to the problems of defining the meaning of abnormal and unsolicited significant abnormal findings. Therefore, this review, which advocates a conservative view toward unsolicited routine chemical screening programs, is presented.

Incidence of Abnormal Findings

The incidence of abnormal findings in any study is influenced by the criteria for normal values and by how an individual report is judged to be abnormal. This alone leads to variations in estimating the incidence of abnormal findings in any survey of data.

The AMA Exhibit Laboratory in 1962 reported on experiences with blood chemistry as shown in Table 1.[1] A breakdown of the distribution of abnormal values is seen in Table 2. One might challenge whether borderline values, such as those for uric acid, should have been included as abnormal findings. Table 3, derived from Young's data, illustrates the possible variations in the interpretation of laboratory data.[2] The incidence of abnormal findings in Young's presentation is modified by considering the day-to-day technical variability commonly observed with these assays. The percent of abnormal findings after modifications is notably different, and this is most pronounced for the electrolytes.

The dilemma of what is abnormal is further illustrated in Table 4, which is based upon information in reports[1,3,4] of AMA Exhibit Laboratory Surveys. Cholesterol assays in 1966 had some

Submitted 2 February 1968.

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recognizable technical problems to possibly explain the change in the incidence of abnormal findings. The decreased incidence in abnormal findings for uric acid in 1965 and 1966 and for glucose in 1966 is most striking, and is not explained. The significance of these abnormal findings is unknown.

Plans are being made to follow up the significance of abnormals from the 1966 AMA survey. The change in incidence of abnormal findings might suggest that the physicians have been successfully treating the chemical abnormalities. This seems unlikely in that there was no striking change between the 1962 and 1965 surveys for glucose and cholesterol. The 1965 high incidence of blood

TABLE 1.—*Findings at AMA Exhibit Laboratory, 1962*[1]

Blood Chemistry	*Number Abnormal*	*Percent of Those Tested*
Elevated serum glucose	378	21
Low serum glucose	1	.06
Elevated serum cholesterol	533	30
Low serum cholesterol	1	.06
Elevated uric acid	632	36
Elevated transaminase	56	3.1
Low serum protein	9	.5
Low serum albumin	10	.5
Elevated alkaline phosphatase	24	1.3
Elevated acid phosphatase	0	0
Elevated serum urea nitrogen (18 or more)	319	18

1,963 chemical abnormalities found in 1,771 physicians. Approximately two-thirds of physicians showed at least one abnormality.

TABLE 2.—*Range of Abnormalities in Blood Chemistry*[1] *at AMA Exhibit Laboratory, 1962*

	Borderline	*Moderate*	*Severe*	*Total*	*Percent*
GLUCOSE mg/100 ml	(120-150)	(151-200)	>200		
Number of physicians	260	95	23	378	21
CHOLESTEROL mg/100 ml	(275-325)	(326-400)	>400		
Number of physicians	404	89	40	533	30
URIC ACID mg/100 ml	(6.5-7.5)	(7.6-8.5)	> 8.5		
Number of physicians	309	194	129	632	36

TABLE 3.—*Interpretative Variation in Incidence of Abnormal Findings*[2]

			Number of Patients				*Corrected**	
Test	*Low*	*Norm*	*High*	*Total*	*Abnormals*	*Percent of Total*	*Abnormals*	*Percent of Total*
Glucose	34	318	37	389	71	18	30	7.5
Urea N	12	320	58	390	70	18	25	6.4
Creatinine	..	364	23	387	23	6	10	3.7
Sodium	85	309	..	394	85	22	6	1.5
Potassium	78	315	..	393	78	20	14	3.6

*Corrected abnormals are estimated by comparing reports with the normal range utilizing a usual value for day-to-day technical variability (±2 SD) to determine abnormality with 95 percent certainty. A result is significantly abnormal if outside the limits of normal range ± the technical variability expressed as ±2 SD.

TABLE 4.—*AMA Exhibit Laboratory Surveys*[1,3,4] *1961 to 1966 Comparisons*

Serum	*Incidence of Abnormal Findings* 1966	*1965*	*1962**
Urea Nitrogen	18%	59.0%	18%
Uric Acid	10%	9.3%	36%
Glucose	4%	17.1%	21%
Cholesterol	3% (18% unsatisfactory)	34.0%	30%
Ca, LDH, SGO-T	1%	—	—
T-3	<1%	—	—
Phosphorus	Normal in practically all persons tested	—	—
Protein; albumin	Normal in practically all persons tested	—	0.5%

*Results for 1961 to 1964 surveys were essentially same.

TABLE 5.—*Distribution of Abnormal Values in AMA Exhibit Surveys*[1,4]

	1962			1965		
	Total Percent Abnormal	*Abnormal Range*	*Number of Patients*	*Abnormal Range*	*Number of Patients*	*Total Percent Abnormal*
Glucose	21	(120-150)	260	(120-159)	343	17.1
		(151-200)	95	(160-200)	36	
		(>200)	19	(>200)	23	
Cholesterol	30	(275-325)	404	(250-300)	553	34
		(326-400)	89	(300-350)	160	
		(>400)	40	(>350)	24	
Uric Acid	*36*	(6.5-7.5)	309	(7.0-8.9)	*211*	17.1
		(7.6-8.5)	194			
		(>8.5)	129	9.0 or >	7	
Urea N	*18*	(>18)	319	(18-25)	970	*59*
				(26-40)	386	
				41 or >	2	

urea nitrogen (BUN) also represents an unexplainable problem of defining normal values in a survey. The distribution of values in comparing 1962 and 1965 surveys does not explain the urea findings in 1965 as noted in Table 5.

The published findings of Thiers[5] are presented in Table 6 and are compared with the 1962 AMA Survey. It is striking that the ambulatory physicians attending a medical meeting are more chemically "sick"—that is, abnormal—than patients being admitted to a general hospital. It is also of interest that the outpatients in Toronto are more "sick" than the inpatients in North Carolina, as illustrated by the incidence of abnormal patients in Table 7. Obviously, then, the designation of an abnormal finding is still clouded by variable criteria and is a subject worthy of additional investigation.

Significant Abnormal Unsolicited Findings

If the problem of determining abnormality is not considered of sufficient moment to some, there is little doubt as to the complexity of the problem when one attempts to determine whether a laboratory finding is necessary or significant for the patient. There have been attempts to evaluate the significance of abnormal findings when these findings are obtained in an unsolicited or routine chemistry screening program. In Thiers' study,[5] 5 percent of inpatients had significant diagnostic abnormal findings, and in Young's study,[2] 2.3 percent of patients had findings which were considered significant as noted in Table 7. Even though both studies included a chemistry panel of ten to eleven tests, about 70 percent of the so-called significant abnormal findings were due to glucose and urea determinations.

In Thiers' study,[5] which initially publicized the application of multi-channel testing, the large multi-channel machine did nine of the tests while a dual channel machine did the glucose and urea determinations. Young's study[2] was further complicated by the fact that only 21 percent of all the patients, who were thought to be significantly abnormal for follow-up, were considered significant after follow-up. Therefore, at least four out of five possibly significant abnormals led to studies which proved the findings to be of no significance and thereby represents a kind of false alarm or

TABLE 6.—*Incidence of Abnormal Tests and Patients Demonstrate that "Well" Physicians are more Abnormal than "Sick" Patients*

Source	*Total Tests*	*Total Patients*	*Total Abnormal Chemistry*	
			Tests	*Patients*
AMA 1962 Survey[1]	17,771	1,771	1,963	*1,181**
Panel: 10 Chemical determinations	Percent of Totals		11	*67*
Duke U.[5]	17,391	1,581	1,080	600
Panel: 11 Chemical determinations	Percent of Totals		6.4	36
Community Hospital[5]	7,062	642	205	154
Panel: 11 Chemical determinations	Percent of Totals		2.9	25
VA Hospital[5]	6,853	623	330	223
Panel: 11 Chemical determinations	Percent of Totals		4.9	36

*These values include all laboratory tests done which include predominantly chemistry studies.

wasted effort working up the patient. Table 8 shows the detailed analysis of outpatient findings from Young's study.[2]

Most clinical pathologists engage in a great deal of discussion with house staff as to whether a test should or should not have been done, and whether or not a result, abnormal or normal, was of significance in providing patient care. A great variation of opinion is most often expressed. This directs one's attention to the fact that significant abnormalities were defined in the Thiers' study[5] by one physician and the pathologist at the VA Hospital. In the Skeggs' study,[6] the designation of unexpected significant abnormal findings was estimated by comparing the abnormal findings with the principal diagnosis obtained by a review of the patient's clinical records.

It is of interest that although there were 149 unexpected abnormal findings noted in Thiers' data[5] (Table 9), only 54 were deemed significant. The uncertainty of data expressivity is evident in that 23 of 28 hyperuricemic findings were considered medically significant, but only four cases of gout were discovered; whereas 16 of 31 abnormal

TABLE 7.—*Significance of Abnormal Unsolicited (Unexpected) Findings*

Source	*Total Patients*	*Unsolicited Abnormals*	*No. of Significant Unsolicited Abnormals*	*Glucose Diabetes*	*Urea Renal Disease*	*Other*	*Comment*
Thiers[5] VA Hospital Inpts. Panel: 11 Chemistries	623	105	31	15	7	9	includes uric acid and cholesterol (1 myeloma)
	% of totals	17	5	2.4	1.1	1.4	
Young[2]	398	211	9	4	3	2	does not incl. uric acid and cholesterol (1 hyperparath?) (1 asthma)
	% of totals	53	2.3	1.0	0.8	0.5	

Toronto General Outpatients Panel: 10 Chemistries

		Analysis of Abnormals				
Total Patients	*Abnormals*	*Expected Confirm Dx.*	*Insufficient Significance no follow-up*	*Biochem. dx. uric acid cholesterol (antibodies)*	*Significant after follow-up*	*Significant for follow-up*
398	211	65	81	23	42	9
% of totals	53	16	20	6	11	2.3

TABLE 8.—*Distribution of Findings from Clinic Outpatient Study*[2]

With usual routine UA, Hgb. and blood film scan, and an extra panel of tests including Glucose, BUN, Creatinine, Sodium, Potassium, Chloride, CO_2 content, Phosphorus, Uric Acid, Calcium (and Sedimentation Rate, Serologic Test for Syphilis, Blood Group and Typing)

Percent	*Number of Cases*	
	398	Total studied
26.0	103	New information normal
18.0	72	New information normal (after at least one value reported was rejected as a lab error or artifact)
16.0	65	Abnormal values reported confirmed the dx.
20.0	81	Abnormal values reported insufficiently significant to require follow-up
5.8	23	Assigned biochem. dx. not needing follow-up (hyperuricemia, hypercholesterolemia, irregular antibody formation)
10.6	42	Abnormal finding seemed of sufficient significance to require follow-up
1.00%	*4*	New information was erroneous
1.00%	*4*	Diabetes mellitus (additional dx.)
0.50%	*2*	Uremia (additional dx.)
0.25%	*1*	Polycystic disease rather than splenomegaly
0.25%	*1*	Asthma and chronic bronchitis substitute for dx. arteriosclerosis
0.25%	*1*	Not followed up
0.25%	*1*	Strongly suspected of hyperparathyroidism
7.30%	*29*	Significance obscure
10.60%	*42*	

TABLE 9.—*Incidence of Unexpected Abnormal Test Results*[5]

	Total	Medically Significant
Glucose	31	16
Urea	7	4
Na	10	0
K	25	1
Cl	2	0
CO_2	6	1
Ca	6	1
Phosphorus	10	2
Protein	15	2
Albumin	9	4
Uric Acid	28	23
Totals	149	54

Note: The large number of unexpected abnormal findings might lead to useless investigations.

TABLE 10.—*OUTPATIENT SURVEY—10 Channels: Serum Sodium, Potassium, Chloride, CO_2 Content, Urea, Glucose Calcium, Protein, Albumin, Phosphatase, Bilirubin, Transaminase* (SGOT)[6]

97 out of 480 patients (20 percent) were abnormal
83 of 97 had medical records examined
66 of the 83 patients revealed unexpected abnormal finding based upon the principle diagnosis
- 15 patients (glucose>150) possible diabetes
- 11 patients mild degree of N retention (urea>20)
- 41 patients with impaired liver function (abnormal bilirubin, and/or alk. phosphatase, and/or SGOT) (Most of patients had diagnoses of hypertension, alcoholism, or schizophrenia; drugs?)
- 5 patients (protein>8.9) elevated serum protein (significance was unexplained)

No follow-up studies confirming significance of abnormal findings are reported

glucose findings were considered medically significant and eventuated in the detection of 15 cases of diabetes mellitus. It is, therefore, apparent from the point of view of clinico-pathologic correlation, that an abnormal glucose finding is more likely to be of clinical significance than a high uric acid finding. Metabolic alterations having no evident clinico-pathologic correlation are really of doubtful or unknown medical significance.

The findings in Skeggs' study[6] reveal the Cleveland outpatients to be chemically healthier (fewer abnormal findings) than the physicians attending the AMA meeting. Table 10 shows that except for the large number of patients with apparently impaired liver function, the major number of significant findings again seems related to glucose and urea determinations.

It is of interest that most of the patients with impaired liver function had histories of hypertension or alcoholism or psychosis, and no mention was made of whether the patients were taking drugs that might possibly explain the chemistry findings. If due to drugs abnormality of liver function tests might represent a transient pharmaceutical chemical event rather than any significant tissue alteration. It is also most disconcerting to notice that follow-up studies to confirm or evaluate the possible significance of these abnormal findings were not done in this study. For example, the significance of urea retention was not evaluated by doing renal clearance studies or creatinine assays, or even a concentration test for renal function in order to ascertain whether it was due to renal disease.

The findings in Table 11 are from an outpatient serum calcium survey.[7] Six hundred out of almost 12,000 patients were classified as abnormal. Of these, only 21 were classifiable as significantly abnormal after repeat assays and additional studies led to a final diagnosis. It should be noted that a parathyroid adenoma was detected in fewer than one patient in 1,000. Review of tables in the article seems to indicate that the diagnosis was suggested in most instances from the clinical findings. Autopsy experiences have revealed up to six adenomas in 76 consecutive autopsies. Therefore, since parathyroid adenomata may be more common than evidenced chemically, when does hypercalcemia occur? When is it important to diagnose hypercalcemia? When again should this population be resurveyed for abnormal serum calcium levels? Studies are definitely needed to determine how often a survey should be repeated.

Other Comments

Chemistry panels and screening examinations may vary, depending upon their purpose. After introducing a 12-channel automated analysis system which included serum electrolytes, the automation manufacturer developed an outpatient diagnostic 12-channel machine which substitutes assays of presumably greater importance than the electrolytes of the original panel. It does seem that the instrument maker or the chemist should not be in the responsible position of deciding on the constituents of chemistry panels or screening. This should be achieved by physicians who are knowledgeable as to the medical needs of patients as well as the financial and technical aspects of the problem.

If present or future medical practice must consider routine chemistry admission studies, these

TABLE 11.—*Routine Serum Calcium Survey Outpatients (after Boonstra)*[7]

	Abnormal Patients 8.8 to 10.4 (95)	*Significant Abnormal**	*Other***
I. Total tests (patients):			
11,991	600	21	539
% of totals	5%	0.21%	4.8%
% of abnormals	—	3.80%	96.0%

*Repeat assays, additional studies, final dx. established.
**After repeat assays: includes technical error, previously established diagnoses, no definite diagnosis.

Total	*Primary hyper-parathyroidism*	*Hypo-parathyroidism*	*Milk alkali syndrome*	*Multiple myeloma*	*Malignancy with bone metastases*	*Hyper-aminoses Vit.-D*
II. Evaluation of patients with the significant abnormal findings:						
11,991	10	3	2	1	5	2
% of total	0.083% (9 adenomas)	0.025%	0.025%	0.008%	0.045%	0.016%

could consist of serum glucose and urea, or creatinine. The development of multi-channel or automated analysis should consider elective pre-operative chemistry studies on major surgical patients. This might include sodium, potassium, chloride, bicarbonate, glucose, urea, protein, transaminase (SGO-T) and bilirubin. An elective diagnostic chemistry survey for patients with medical diagnostic problems could also include serum calcium, protein-bound iodine, alkaline phosphatase, uric acid, and cholesterol, as well as the constituents of the pre-operative chemistry studies. A renal function panel could include serum urea nitrogen, creatinine, sodium, potassium, chloride, and carbon dioxide content. A liver function panel could consist of serum total and direct bilirubin, alkaline phosphatase, transaminase, and prothrombin time. These represent only some of the grouping that could be considered in the best interest of good laboratory medicine rather than in terms of instrument or instrument manufacturers' convenience. An appropriate chemistry panel requisitioned by a physician for a particular patient rather than the routine indiscriminate application of the machine to a patient's blood specimen, will be in the best interests of progressive and good medicine.

In a most recent article Rardin[8] reported experiences with laboratory profile screening in the physician's office. Review of this paper reveals that out of 18,300 tests done, there were 257 (1.4 percent) in which results were reported as medically significant. Medical significance was defined as data which confirmed a known disease or led to a new or more complete diagnosis. Based upon usual experiences, it is probable that unexpected significant abnormal findings are fewer than expected findings and, therefore, only represent about 0.3 to 0.15 percent of the tests done. No attempt was made in the paper to indicate how many patients rather than tests might be involved with unexpected significant findings revealed by the survey.

In conclusion, the following reflections are offered. They are based upon the review of chemistry screening surveys presented in this paper and the ill-defined criteria for normal, abnormal and significantly abnormal findings.

- The need for further efforts to define what is significantly abnormal is most evident. This is exemplified by the fact that ambulatory physicians attending medical meetings are "more sick" (more abnormal) than the patients they have been admitting for hospitalization or seeing as outpatients attending a general hospital clinic.

- Significant unsolicited abnormal findings have been reported in from 2 to 5 percent of patients studied. Approximately 70 percent of these so-called significant abnormal unsolicited chemistry findings are related to blood glucose and urea. These determinations have been recommended for many years by some physicians as part of the routine medical examination. Nine to ten additional chemistry tests led to detecting only approximately 30 percent of the apparently significant unsolicited findings, and this represented less than 1 or 2 percent of patients studied.

- Unsolicited *abnormal* chemistry findings lead to a great deal of additional studies. Approximately 80 percent of the time, these lead to conclusions having no clinical significance for the patient.

• Even when chemistry studies are not done routinely but are ordered as clinically indicated, their significance is difficult to evaluate. This has always been a problem. Interns and residents are often accused of ordering too much laboratory work as compared with the sophisticated attending physician. The general consensus in the field of laboratory medicine used to be that we obtain plenty of data, and that the major problem is the interpretation of findings. We should avoid exaggerating this problem by introducing overwhelming amounts of useless information.

• Little information, if any, is available as to how often the chemistry screening examination should be repeated for a given individual, or for a specific population of patients.

• We should be reserved and careful in the application of laboratory screening methods to avoid what might be the fostering of "decerebrate"[9] rather than good laboratory medicine.

• Predictive medicine and diagnostic automated chemistry screening panels seem to be an exciting challenge in the field of clinical pathology. These concepts deserve and require a great deal more experience and research before uniform measures should become generally acceptable to physicians, patients and politicians.

ADDENDUM: Some interesting comments confirming some of the impressions referred to in this paper are evident in the Editorial entitled "Who's for Screening?" in the 30 September 1967 issue of *Lancet*, page 706.

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CONFIRMING A DEBATABLE LUNG CANCER

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Audio-Digest *General Practice*, Vol. 16, No. 12